Addiction & Recovery 2023
the latest findings from neuroscience research

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The Neuroscience of Addiction in 2023

Presented by: Kevin McCauley, MD

CO-OCCURRING DISORDERS: Self-Medication Pathways into Addiction

12-month prevalence of Substance Use Disorder in persons with MDD is 12 – 30%

STRESS: Stress & Trauma Pathways into Addiction

Among treatment-seeking persons with SUD, 30-50% also meet criteria for PTSD (lifetime), and among persons with PTSD, are 4 to 5 times more likely to have SUD (lifetime).

OPIOID EXPOSURE: Pain Management Pathways into Addiction

“Surgery may unmask an individual’s susceptibility toward long-term opioid use” (Sun et al., 2016)

Factors associated with increased risk of chronic opioid use
- preoperative use of benzodiazepines
- preoperative use of antidepressants
- history of Substance Use Disorder
- history of Alcohol Use Disorder


Is Addiction Really a “Disease?”

What is a "model?"

- Theory: an explanation of the natural world based on observations that explains known facts and allows predictions (hypotheses) that can be tested
- Theories test their hypotheses using models
- Model: a human-created representation of a natural phenomenon (ex. an object, person or system) informed by a theory
- Models can be physical (ex. model airplane in a wind tunnel) or abstract (ex. mathematical or statistical models) or conceptual (ex. medical model used by clinicians or Standard Model used in physics)
- A model is not the actual thing – it will not fit the natural phenomenon perfectly
- Any time you switch from one model to another you gain and lose explanatory and predictive power but your factual observations may become more valid and your predictions more accurate
Different Models Used to Explain Addiction

- Moral Model of Addiction
- Personality Model of Addiction
  - affect dysregulation
  - reinforcement sensitivity
  - impulsivity/behavioral disinhibition
- Neuropsychologic Model of Addiction
- Learning Model of Addiction
- Life Course Model of Addiction
- Neuropathophysiologic Model of Addiction (aka Medical Model)

Public Health Model of Addiction

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From the “Disease Model” of Addiction ... 
... to a “Public Health/Ecological Model” of Recovery

The Public Health Model of Recovery
- life course
- educational opportunity
- societal context
- housing
- identity
- disparity
- family
- social support
- occupation
- cultural context
- faith, meaning and purpose
- political context
- detox & treatment

The Disease Model of Addiction
- medication
- mental health
- primary care

Less reductive
& can account for
Social Determinants of Health
Health Inequities & Health Injustice

all the causal power of the Disease Model is contained within the Public Health Model ... it is not possible to simultaneously make the argument that addiction is not a disease and advocate for a Public Health approach to addiction.
What is craving?

• A feeling?
• An emotion?
• A thought (cognition)?
• A mood (affect)?
• An action?
• A relationship?
• Frustration? Yearning? Grieving? Attachment?

Cognition does not just take place in the brain, it is ...

1. EMBODIED
   the body shapes cognition

2. EMBEDDED
   cognition causally exploits objects in the environment and the physical/social/historical environment shapes cognition

3. EXTENDED
   the tools and affordances that enable agency also shape cognition

4. and ENACTED
   our actions in the world determine our cognitions
Addiction is a disease of volition

Volition: response to a challenge to homeostasis

- what is the need? conscious? / unconscious?
- how do interpret that need? interoceptive accuracy?
- what strategies can I recall that would meet the need? memory?
- which strategy do I select? calculation: value/probability
- what is my plan? what are my resources? affordances/tools
- the actual motoric input to effect the world? agency
- what is the result? did my plan of action work?
- what is the world's response to my act? social consequences?
What does it mean to have a disease of “volition?”

What would it be like if such a disease could occur?

- Hurts
- Deformity / Trauma
- Disability
- Want to get up and run (can’t)
- Confusion when can’t
- Tx: fixation / immobilization
- Healing / Physical therapy
- +/- Lifelong vulnerability
What would it be like if there could be a such thing as a "volitional disorder?"

**Broken Leg**
- Hurts
- Deformity / Trauma
- Disability
- Want to get up and run (can’t)
- Confusion when can’t
- Tx: fixation / immobilization
- Healing / Physical therapy
- +/- Lifelong vulnerability

**Volition**
- Emotional/Spiritual pain
- Unmanageability
- Phys/Psych/Soc/Occupational Consequences
- “Countless attempts” to make it work
- “Bafflement” when it doesn’t
- Tx: “Turning over one’s will & life”
- Graduated exercises of volition
- Volitional segregation (Serenity Prayer)

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**Serenity Prayer … volitional segregation**

God,  
grant me the serenity  
to Accept the things I cannot change  
Courage to change the things I can  
and  
Wisdom to know the difference

Reinhold Niebuhr (1892 – 1971)  
Theologian (Christian Realism)
ASAM Addiction Definition (2011)

Addiction is a primary, chronic disease of brain reward, motivation, memory and related circuitry characterized by
1. inability to consistently abstain
2. impairment in behavioral control
3. craving
4. diminished recognition of significant problems with one’s behaviors and interpersonal relationships,
and a
5. dysfunctional emotional response


ASAM Addiction Definition Updated (2019)

- Addiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual’s life experiences.
- People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.
- Prevention efforts and treatment approaches for addiction are generally as successful as those for other chronic diseases.

Addiction is a disorder in the brain’s hedonic system (pleasure sense).

...undermining the individual’s decision-making capacity (choice) and self-awareness (insight).
ASAM Addiction Definition (Aug 2011)

A stress-induced (HPA axis, microbiome, immune syst), genetically-mediated (polymorphisms, epigenetic mechs.) primary, chronic brain disease of reward (nucleus accumbens), memory (hippocampus & amygdala), motivation and related circuitry (ACC, OFC, Insula) that alters motivational hierarchies such that addictive behaviors supplant healthy, self-care behaviors
What goes into a pleasurable experience?

“Yum!”

Frontal Cortex:
- PFC: Prefrontal Cortex
  - executive functioning
  - behavioral inhibition
- ACG: Anterior Cingulate Cortex
  - social cognition
  - error detection
- OFC: Orbitofrontal Cortex
  - valuation under shifting conditions of uncertainty

Stress Areas:
- Hypothalamus (HPA Axis)
- Pituitary Gland
- Adrenal Glands

Memory/Learning Areas:
- Hipp: Hippocampus
  - memory formation
- Amyg: Amygdala
  - fear conditioning

Reward/Salience Areas:
- NAc: Nucleus accumbens (ventral striatum)
- VP: Ventral Pallidum
- VTA: Ventral Tegmental Area (midbrain)
**Diffusion Tensor Imaging (a form of MR imaging)**

**Reward/Salience Areas:**
- **NAc:** Nucleus accumbens (ventral striatum)
- **VTA:** Ventral Tegmental Area (midbrain)

**MIDBRAIN**
(survival “engine”)
What goes into a pleasurable experience?

- Cake ensures survival
- Cake tastes good

Reward/Salience Areas:
- NAc: Nucleus accumbens (ventral striatum)
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Dopamine Neurotransmission

Reward/Salience Areas:
- **NAc**: Nucleus accumbens (ventral striatum)
- **VTA**: Ventral Tegmental Area (midbrain)

1. Survival Salience

Reward: overvaluation drug = survival

DOPAMINE

Reward: overvaluation drug = survival
What goes into a pleasurable experience?

- Cake tastes good
- Cake ensures survival
- Memory of this cake
- Memories of past cakes

The “Brain Reward Cascade” (Blum)

#1. Dopamine

Reward Salience

#2. Glutamate

1. Reward Learning
2. Cortical Control

Consummatory “Pleasure”
“Yum!”

- Endogenous Opioids
- Endogenous Cannabinoids
- GABA
- Serotonin
- Oxytocin

Adapted from:
Blum K, Ebb M, Badalwan RD. Fifty years in the development of a glutamergic-dopaminergic optimization complex (KBl220) to balance brain reward circuitry in reward deficiency syndrome: a pictorial. Austin Addict Sci; 2018/12/
What goes into a pleasurable experience?

- Cake tastes good
- Cake ensures survival
- Memory of this cake
- Memories of past cakes
- Cake solves hunger
Stress Areas:
- Hypothalamus
- Pituitary
- Adrenal
- Axis

CRF

MIDBRAIN (Dopamine)

CRF Stress

Homeostasis

Dopamine
Stress Areas:
- Hypothalamus
- Pituitary
- Adrenal Axis

VTA

MIDBRAIN (Dopamine)

CRF

3. Over-Used

Stress: drug is most efficient stress-coping strategy (i.e. the drug has utility)
What goes into a pleasurable experience?

- Cake tastes good
- Cake ensures survival
- Memory of this cake
- Memories of past cakes
- Cake solves hunger
- Emotions about cake
- Meaning of cake (Grandma’s?)
- Choices about cake (2nd piece?)

Frontal Cortex:
- **PFC**: Prefrontal Cortex
  - executive functioning
  - behavioral inhibition
- **ACG**: Anterior Cingulate Cortex
  - social cognition
  - error detection
- **OFC**: Orbitofrontal Cortex
  - valuation under shifting
  - conditions of uncertainty

Insular Cortex – interoception
Addiction is a disorder of ...

<table>
<thead>
<tr>
<th>5. CHOICE</th>
<th>OFC, ACC, PFC, IC</th>
<th>Pathology of Motivation and Choice (Volkow, Goldstein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. STRESS</td>
<td>HPA axis</td>
<td>Stress-induced Allostasis, Negative Emotional States (Koob &amp; LeMoal)</td>
</tr>
<tr>
<td>3. MEMORY</td>
<td>glutamate</td>
<td>Glutamate Homeostasis &amp; “Spillover” (Kalivas)</td>
</tr>
<tr>
<td>2. REWARD</td>
<td>dopamine</td>
<td>Dopamine-signaling and Incentive-Sensitization (Volkow, Berridge &amp; Robinson)</td>
</tr>
<tr>
<td>1. GENES</td>
<td>polymorphisms</td>
<td>Genetic and Epigenetic vulnerability &amp; resilience (Schuckit, Kandel &amp; Kandel)</td>
</tr>
<tr>
<td></td>
<td>epigenetic changes</td>
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</tbody>
</table>
DSM-5 Criteria for “Substance Use Disorder”

(2 or more in the last year)

1. **IMPORTANT ACTIVITIES** are given up in favor of the drug
2. **PHYSICAL & PSYCHOLOGICAL PROBLEMS** due to drug do not curtail use
3. **SOCIAL & INTERPERSONAL PROBLEMS** due to drug does not curtail use
4. **INABILITY** to cut down or control drug use
5. **LARGER AMOUNTS** of drug used over **LONGER PERIODS** than intended
6. **A LOT OF TIME** spent obtaining, using & recovering from drug use
7. **HAZARDOUS** situations occur involving drug use
8. **FAILURE TO FULFILL** work, school, & home obligations due to drug use
9. **CRAVING**
10. **WITHDRAWAL**
11. **TOLERANCE**

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How does Addiction (SUD) run in families?
What is the genetic component of Addiction (SUD)?

Addiction is a disorder of ...

1. GENES  polymorphisms
2. REWARD  dopamine
dopamine receptors
3. MEMORY  glutamate
    synaptic remodeling
4. STRESS  HPA axis
5. CHOICE  OFC, ACC, PFC, IC
Heritability of Addiction
(from twin studies)

- Alcohol: 48 – 66%
- Cannabis: 51 – 59%
- Cocaine: 42 – 79%
- Opioids: 23 – 49%
- Nicotine: 33 – 71%
- Gambling: 49%

- Heritability: an aggregate measure of the variability of a characteristic due to genetics vs environment (the risk due to genes – “risk genes”)
- First-order family members of a person with SUD have a 4 – 8 x increased risk of developing SUD
- Applies to populations, not individuals (that would be inheritance)
- Probabalistic, not deterministic


Taq1 A1 allele of the DRD2 gene
(Blum & Noble, 1990)

A single nucleotide polymorphism the carriers of which have 30-40% fewer DAD2 receptors and are at high risk for:
- Alcoholism and Addiction
- Repeated addiction treatment failures
- Increased mortality from alcoholism
- Lower striatal DAD2 receptor availability and lower striatal DA binding potential

Social Determinants of Health:
conditions in the environment in which people are born, live, learn, work, play, worship, and age that affect a wide range of health, functioning and quality of life outcomes and risks

Health Disparities:
systemic, avoidable health differences adversely affecting socially disadvantaged groups; different from health differences

Health Equity:
a commitment to reduce/eliminate health disparities; social justice with respect to health; equal opportunity to be healthy

Healthy People 2020 Approach to SDHs

https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health
Social Determinants of Health

<table>
<thead>
<tr>
<th>Social Determinant of Health</th>
<th>Health Disparity</th>
<th>Health Inequity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety</td>
<td>early life adversity (ACEs)</td>
<td>chronic disease, shorter lifespan</td>
</tr>
<tr>
<td>2. Healthy Food</td>
<td>low availability, food deserts</td>
<td>higher diabetes, obesity</td>
</tr>
<tr>
<td>3. Income Security</td>
<td>poverty, lack of social safety net</td>
<td>chronic disease, shorter lifespan</td>
</tr>
<tr>
<td>4. Housing</td>
<td>housing insecurity / rent as % of income</td>
<td>higher asthma, lead exposure</td>
</tr>
<tr>
<td>5. Education, Job Training</td>
<td>lower HS graduation rates</td>
<td>unhealthy behaviors (smoking)</td>
</tr>
<tr>
<td>6. Social / Family Support</td>
<td>isolation, intimate partner violence (IPV)</td>
<td>greater depression &amp; suicide</td>
</tr>
<tr>
<td>7. Community</td>
<td>stigma, racism, discrimination</td>
<td>inaccessible services &gt; chron dis.</td>
</tr>
<tr>
<td>8. Employment</td>
<td>unemployment, lack of opportunity</td>
<td>chronic disease, suicide, SUD</td>
</tr>
<tr>
<td>9. Access to Health Care</td>
<td>ineligibility / work requirements</td>
<td>ex. less cancer screening</td>
</tr>
<tr>
<td>10. Justice</td>
<td>disprop. policing / mass incarceration</td>
<td>chronic disease, shorter lifespan</td>
</tr>
</tbody>
</table>

http://thenationshealth.aphapublications.org/content/infographics-social-determinants-health

Epigenetics

- Overkalix study: Starvation during adolescence increased the prevalence of diabetes in **grandchildren**
- Holocaust survivors with PTSD: their children also had PTSD without having been exposed to trauma
- A mechanism exists to transmit environmental exposure information from one generation to the next to the next
Food Scarcity

the stressors faced by one generation can have transgenerational influence on disease expression (ex. Trauma may be heritable)

EPIGENETIC MECHANISMS
- Development (in stress, childhood)
- Environmental chemicals
- Drugs/Pharmacotherapies
- Aging
- Diet

HEALTH ENDPOINTS
- Cancer
- Autoimmune disease
- Mental disorders
- Diabetes

Histones are proteins around which DNA can wind for compaction and gene regulation.

DNA methylation
Methyl group (an epigenetic factor found in some dietary sources) can tag DNA and activate or repress genes.

Histone modification
The binding of epigenetic histones to histone “tails” alters the extent to which DNA is wrapped around histones and the availability of genes in the DNA to be activated.
How does what we know about genetics help me get sober?

- Genes are a powerful influence on our behavior (voluntary and involuntary) and our choices
- Epigenetics, too, deepens our understanding of how we make choices in response to environmental stressors
- But genetics and epigenetics do not solely determine our behaviors and choices
- We can “acquire” resiliency in recovery to offset our genetic vulnerability
- Epigenetics provides a mechanism by which recovery can be heritable, too

What causes the Persistent Use Despite Negative Consequences symptom of Addiction (SUD)?
Addiction is a disorder of...

1. GENES polymorphisms, epigenetic changes
2. REWARD dopamine, dopamine receptors
3. MEMORY glutamate, synaptic remodeling
4. STRESS HPA axis
5. CHOICE OFC, ACC, PFC, IC

What goes into a pleasurable experience?

"Yum!"
James Olds, PhD (1922 - 1976)
Peter Milner, PhD (1919 – 2018)

- Discovery of the reward system through intracranial self-stimulation in rats
- Mice will avidly self-administer electric currents to the Septal Areas of the brain
- They prefer the electrical stimulation over other survival rewards such as food (a drive state independent of other drive states such as hunger)


Reward/Salience Areas:
- NAc: Nucleus accumbens (ventral striatum)
- VP: Ventral Pallidum
- VTA: Ventral Tegmental Area (midbrain)
**in vitro micro-dialysis**

- **Microdialyte**
- **Rollerpump**
- **Probe**
- **Semi-permeable membrane**

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**Drugs of abuse increase synaptic dopamine in the mesolimbic system of rats**

"The present results show that drugs belonging to different pharmacological classes but sharing the characteristic of being rewarding in animals and humans share the properties of preferentially increasing synaptic dopamine concentrations in the mesolimbic dopaminergic system and of stimulating behavior."

- D’Chiara & Imperato, 1988
Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of incentive/reward salience (survival importance)
Incentive-Salience 
(Berridge & Robinson)

- Distinguished between a “liking” and a “wanting” role for Dopamine (it’s more about “wanting”)
- Created hyper-dopaminergic Dopamine Transporter “knock-down” mice (mice with increased synaptic Dopamine)
- Observed increased intake of reinforcing substances in these mice and greater thwarting of obstacles to get them (i.e. more “wanting”)
- But did not observe greater “liking” of these substances by these mice

Addiction Neurochemical #1: Dopamine

- All drugs of abuse and potential compulsive behaviors release Dopamine
- Dopamine is the first chemical in the cascade of chemicals that generate a rewarding experience
- DA is the chemical of incentive/reward salience (survival importance)
- DA is more about “wanting” than “liking”
- DA is more about expectation than consummation
- DA signals reward prediction error - it tells the brain when something is “better than expected”
DA NAc neurons do more than encode receipt of reward

- Amount of reward
- Motivation/Incentive Salience of reward
- Errors in reward prediction
- Expectancy of reward
- Delay of reward
- DA NAc neurons contribute to synaptic neuroplasticity that underlies the acquisition of addictive behaviors


Dopamine: also for bad things

- Kutlu et al (2021): KCS Model – DA handles prediction error, association formation, attention, temporal dynamics
- Reward Prediction Error seen in specific reward learning contexts but not seen in aversive learning contexts
- Dopamine seen in neutral learning contexts, especially ones that are new (novel)
- Dopamine codes for a valence-independent perceived saliency (scaled physical intensity of a stimulus)

The “Ns” of Dopamine

<table>
<thead>
<tr>
<th>Dopamine encodes for things that are:</th>
<th>meaning</th>
<th>example</th>
</tr>
</thead>
<tbody>
<tr>
<td>“N-bayable”</td>
<td>rewarding stimuli</td>
<td>the core component of a hedonic (pleasurable) experience</td>
</tr>
<tr>
<td>“N-centivized”</td>
<td>incentive, motivational drive</td>
<td>wanting &gt; liking</td>
</tr>
<tr>
<td>Novel</td>
<td>first exposure</td>
<td>magnification of learning of new &amp; relevant experiences</td>
</tr>
<tr>
<td>Noxious</td>
<td>aversive stimuli</td>
<td>re-experiencing of traumatic events</td>
</tr>
<tr>
<td>Neutral</td>
<td>valence-independent stimuli</td>
<td>association with otherwise unrelated sensory &amp; emotional cues, cunning/baffling/powerful nature of cue-induced relapse</td>
</tr>
<tr>
<td>Near-misses</td>
<td>reward prediction error</td>
<td>illusion of “better than expected” value, mis-remembering past intoxication episodes, chasing losses</td>
</tr>
<tr>
<td>Nearby</td>
<td>proximal, imminent</td>
<td>near in space and/or time; fantasy and fictive imagining; failure of delay discounting; craving</td>
</tr>
<tr>
<td>Numerated</td>
<td>number, amplitude, counts</td>
<td>social media “likes,” hoarding (collection/accumulation addiction)</td>
</tr>
</tbody>
</table>

Glutamate inputs (e.g., from cortex)

Alcohol

PCP

Stimulants

Nicotine Alcool

Opioid peptides

VTA interneuron

GABA

DA

NAc

VTA

Glutamate inputs (e.g. from amygdala)
Dopamine, Dopamine Receptors and Addiction

- Drugs of abuse cause supraphysiologic increases in extracellular dopamine in the striatum that correlate with subjective feelings of being “high”
- PET scan studies: impaired striatal dopamine signaling due to decreased DAD2 receptors
- fMRI scan studies: brain activation abnormalities in striato-cortical pathways that regulate reward, self-control, and affect
- Overlap in brain circuitry underlying addiction and disorders such as binge eating and pathological gambling
- Other brain chemicals matter, too (glutamate, GABA, endogenous opioid and cannabinoids)

Nora D. Volkow, MD
Director, National Institute on Drug Abuse


Dopamine-Releasing Chemicals

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids

Dopamine-Releasing Behaviors

- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
  ("Codependency," Control)
- Gambling
- Cults
- Performance
  ("Work-aholism")
- Collection/Accumulation
  ("Shop-aholism")
- Rage/Violence
- Media/Entertainment
The Neuroscience of Addiction in 2023

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The Full Spectrum of “Intoxication”

- Alcohol & Sedative/Hypnotics
- Opiates/Opioids
- Cocaine
- Amphetamines
- Entactogens (MDMA)
- Entheogens/Hallucinogens
- Dissociants (PCP, Ketamine)
- Cannabinoids
- Inhalants
- Nicotine
- Caffeine
- Anabolic-Androgenic Steroids
- Food (Bulimia & Binge Eating)
- Sex
- Relationships
- Other People
  - (“Codependency,” Control)
- Gambling
- Cults
- Performance
  - (“Work-aholism”)
- Collection/Accumulation
  - (“Shop-aholism”)
- Rage/Violence
- Media/Entertainment

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Periodic Table of the Intoxicants
How does what we know about reward help me get sober?

- All intoxicants (chemicals and behaviors) cause large and fast dopamine releases in brain reward structures which is toxic to dopamine receptors.
- I may have had a dysfunctional dopamine system prior to using drugs (examples include be “Reward Deficiency Syndrome” and ADHD).
- By avoiding intoxication I can restore the number and function of my dopamine receptors.
- This may mean avoiding cross-addicting chemicals and behaviors like nicotine and sugar.
- Practicing normal pleasurable activities restores my brain’s ability to respond to normal pleasures normally (hedonic rehabilitation).

What causes the Relapse symptom of Addiction (SUD)?
Things that cause Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc)
     drug-induced reinstatement DOPAMINE
  2. Exposure to drug cues (GLU release in Amygdala/Hipp)
     cue-induced reinstatement GLUTamate

Addiction is a disorder of ...

5. CHOICE OFC, ACC, PFC, IC
4. STRESS HPA axis
3. MEMORY glutamate synaptic remodeling
2. REWARD dopamine receptors
1. GENES polymorphisms epigenetic changes
Addiction Neurochemical #2: Glutamate

- The most abundant neurochemical in the brain
- Critical in memory formation & consolidation
- All drugs of abuse and many addicking behaviors effect Glutamate which preserves drug memories and creates **drug cues**
- And ... glutamate is the neurochemical of “motivation” (it initiates **drug seeking**)

Adapted from:
Glutamate “spillover”

- Enduring vulnerability to relapse due to recruitment of “corticofugal” GLU projections to striatum
- Excess GLU “spills” out of the synapse to bind to extra-synaptic GLU receptors
- Changes in synaptic plasticity leads to pathologic learning and memory
- Result: impairment of inhibition of drug seeking

Peter W. Kalivas, PhD
Department of Neurosciences
Medical University of South Carolina
Glial Cells

- Caretaker cells of the CNS & PNS
- Half the total volume of the brain
- Equal number as neurons (in Cortex: 4 glial cells to each neuron)
- Can divide as adult cells

Memory/Learning Areas:
- Hipp: Hippocampus - memory formation
- Amyg: Amygdala - fear conditioning, early emotion

Learning: drug hyper-memories drug cues > relapse
How does what we know about memory help me get sober?

- Sensory and Environmental Cues are powerful relapse triggers of which we are not always conscious
- Relapse Prevention Strategy:
  - caution with people, places and activities previously associated with drug use
  - self-talk of Cognitive-Behavioral Therapy can strengthen commitment to sobriety (improve cortical inhibition)
  - Medications that stabilize glutamate (Acamprosate – Campral ©) or provide opioid receptor blockade (Extended-release Naltrexone – Vivitrol ©) can provide a margin of safety to avoid or minimize relapse

Things that cause Relapse

- Persistent relapse / and risk thereof
- Even after periods of abstinence
- Triggered by:
  1. Re-exposure to drug itself (DA release in NAc)  
     - drug-induced reinstatement  
     - DOPAMINE
  2. Exposure to drug cues (GLU release in Amygdala/Hipp)  
     - cue-induced reinstatement  
     - GLUTAMATE
  3. Exposure to Envir Stress (CRF release in Amygdala)  
     - stress-induced reinstatement  
     - CRH, DYNORPHIN, etc
What causes the *Loss of Control* symptom of Addiction (SUD)?

Addiction is a disorder of ...

1. **GENES**
   - polymorphisms
   - epigenetic changes

2. **REWARD**
   - dopamine receptors

3. **MEMORY**
   - glutamate synaptic remodeling

4. **STRESS**
   - HPA axis

5. **CHOICE**
   - OFC, ACC, PFC, IC

[Image of brain regions labeled with functions: OFC, ACC, PFC, IC, OFC, SCC, NAC, VP, Amygd, Hipp, Motivation/Drive, Memory/Learning, Inhibitory Control, Reward/Salience]
Hedonic Allostasis Theory
(Koob & LeMoal)

- With continued drug use and withdrawal, the “anti-reward” system is recruited to *counter-balance* excess Dopamine using the stress hormone CRF
- Brain is unable to maintain normal “homeostasis”
- So the brain reverts to “allostasis” - change of the hedonic “set point” under stress in an attempt to maintain stability
- The result is anhedonia – an inability to find pleasure in normally pleasurable activities

**Hedonic Allostasis Theory**

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**A-process:**

drugs activate brain circuits that elicit pleasurable emotional states (reward)...

[Graph showing reward thresholds for different stimuli over length of access]
B-process:
... counter-regulatory stress hormones to restore affective/emotional homeostasis

Stress Areas:
- Hypothalamus
- Pituitary
- Adrenal Axis
- VTA

Stress Hormones:
- CRH (Corticotropin-releasing hormone)
- ACTH (Adrenocorticotropic hormone)

Stress Areas:
- Midbrain (Dopamine)
- Hypothalamus
- Pituitary
- Adrenal Axis

CRF

INHIBITORY CONTROL

ACG

PFC

GFC

SCC

NAC

Hypothalamus

Pituitary Gland

MEMORY/LEARNING

MOTIVATION/DRIVE

REWARD/SALIENCE

C R F

Stress Areas:
- Hypothalamus
- Pituitary
- Adrenal Axis
The Hypothalamic Pituitary Adrenal (HPA) Axis

CRH - Corticotropin-releasing hormone
ACTH - Adrenocorticotropic hormone

All of these pathways pass through and are affected by ...

Genetics / Epigenetics (e.g. Taq1A1 allele)
Depression / Anxiety Other Mental Illness
Early Use / Peer Use / Parental Use
Trauma / P.T.S.D.
Adverse Childhood Experiences
Chronic Pain
Prescribed Medication
Cortical Dysfunction
Psycho-neuro-immunology

- A way to understand how stress and trauma cause mental illness through the immune system
- The Immune-Brain Loop: immune system is in constant communication with the brain; the immune system is a stress receptor for the brain
- CNS neurons terminate in thymus and spleen near clusters of lymphocytes and macrophages
- Adler & Cohen (1975): conditioned rats to drink saccharin water & Cytoxan (an immunosuppressant drug that tastes bad); later when they drank saccharin water the rats died of infection (immunosuppression in the absence of Cytoxan)
- Visintainer (1983): inescapable tail shock associated with decreased lymphocyte proliferation & decreased tumor rejection

Glial Cells

• Caretaker cells of the CNS & PNS
• Half the total volume of the brain
• Roughly equal number of glial cells as neurons
• Can divide as adult cells

Microglia

• Predominant immune cells of the CNS
• Cover a specific territory
• Usually in resting (ramified) state
• Secrete Brain-Derived Neurotrophic Factor (BDNF)
• Assist neuronal circuit remodeling across development (synaptic pruning)
• Responsible for CNS homeostasis and plasticity
**Reactive Microgliosis: response to pathogen/injury**

- Resting microglia: injury to the brain triggers Reactive Microgliosis
- Microglia respond rapidly to stress and trauma
- Shift from ramified (resting) state to ameboid (activated) state
- Microglia are very fast-moving cells (fastest in the brain: entire brain parenchyma scanned by microglia every few hours)
- Become macrophages > phagocytize pathogens and debris
- Antigen-presenting cell to T lymphocytes

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**How does what we know about stress help me get sober?**

- **Proactive Stress Management** (ex. relapse plan)
- **Peer-based recovery support** integrates sobriety modeling and norms, recovery-oriented systems of care resources, and peer coping build social capital, recovery capital, and resilience
- **Contingency Management** (an Evidence-Based Practice) stops treatment cycling
- **Safe Housing**: a critical social determinant of health and recovery
- **Trauma-informed Therapy** can prevent long-term problems
- **Immune system support** decreases stress-related inflammation (ex. sleep, diet, gut microbiome)
- **Medications can help**: examples include MAT/MOUD and meds to decrease sympathetic discharge (*Clonidine*)
What causes Craving, Impaired decision-making, Loss of insight, and Emotional dys-regulation symptoms of Addiction (SUD)?

Addiction is a disorder of ...
Frontal Cortex:
PFC: Prefrontal Cortex  
- executive functioning  
- behavioral inhibition  
ACG: Anterior Cingulate Cortex  
- social cognition  
- error detection  
OFC: Orbitofrontal Cortex  
- valuation under shifting conditions of uncertainty  
Insular Cortex – interoception


Correlations Between D2 Receptors in Striatum and Brain Glucose Metabolism

Anterior Cingulate Cortex (ACC)

- Conflict monitor; discrepancy “alarm”
- Inhibition of goal-directed behavior
- Social cue detection
- Self-monitoring in social situations
- Rostral ACC: emotional processes, expected pain/social rejection
- Dorsal ACC: cognitive processes, unexpected pain/social rejection
- fMRI: active in tasks requiring empathy and trust; engaged in cognitive tasks requiring attention

Damage to the Anterior Cingulate Cortex (ACC)

- Loss of a crucial behavioral guidance system
- Inflexibility in responding / Inability to respond to errors in the past with regard to rewards & punishments
- Deficits in social responding due to decreased awareness of social cues
- Impulsivity and perseverance increases
**Orbitofrontal Cortex (OFC)**

- Decision-making guided by rewards; integrates sensory and emotional information from lower limbic structures
- Encodes outcome reward value and probability of possible expected outcomes (rapidly and subconsciously calculates likelihood of an outcome)
- Flexible enough to account for incoming new information
- Motivates or inhibits choices & actions
- Self-monitoring and social responding

**The Brain is a Bayesian Calculator**

\[
P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)}
\]

Rev. Thomas Bayes (1701 – 1761)
damage to the
Orbitofrontal Cortex (OFC)

- Like damage to ACC, also causes a loss of a crucial behavioral guidance system
- Responses are impulsive and inappropriate
- Deficits of risk assessment and self-regulation
- Tendency to choose small & intermediate rewards over larger but delayed rewards (worsening of delay discounting)
- Inability to properly assign value and outcome probability to appropriate rewards (such as money vs. drugs)

In addiction, the brain’s ability to correctly calculate

1. value
   and
2. probability
becomes severely biased

This means that people in early recovery have a hard time assessing the likelihood of future harm

... or RISK
The Problem:
How can I protect myself from relapse (decision-making) when my ability to assess relapse risk is itself impaired (loss of insight)?

How does what we know about choice help me get sober?

- Abstinence from intoxication and practicing normal, healthy rewarding activities repairs and strengthens the dopamine system and signaling to the frontal cortex
- Peer-based stress coping, social connectedness, and mindful reflection improve the function of the frontal cortex
- Agency-building exercises improve self-efficacy
- Mutual Support Group attendance that involves service work, working with newcomers, & taking commitments decrease self-centeredness
- Purposeful, meaningful goals decrease shame, increase self-forgiveness, and improve the chances of entering long-term recovery
- Once safe, returning to work or school and practicing occupational/vocational skills stabilizes long-term recovery and give the person a future
An Effective Recovery Management Plan

1. Treatment (Residential or IOP) - evidence-based treatment, enculturation
2. Therapist/Counselor/Coach - ongoing f/u, advocacy, ROSC linkage
3. Recovery Residence - housing security, peer support
4. Mutual Support Groups - social connectedness, social narrative
5. Relapse Plan - contingency management
6. Testing - chronic disease monitoring, parity
7. Job/School/Future - educational / vocational opportunity
8. Addiction Medicine Specialist - access to longitudinal primary care
9. Medication - MAT, nicotine cessation, etc.
10. Hedonic Rehabilitation - community recreation & leisure activities

Common challenges to the Conceptualization of Addiction as a Disease

- There’s no evidence that addiction is a brain disease ...
- ... and there have been no advances in treatment based on brain research
- Most people mature out of their addictions
- Drug use is situational (Vietnam Vets & heroin study)
- Drugs don’t cause addiction (Rat Park study)
- We’re all addicted to something
- It doesn’t matter if we call it a disease or not ...
Discrepant findings for which the Disease Model must account....

- **Lee Robins (Vietnam Vets)**\(^1\): drug use is situational
- **Bruce Alexander (Rat Park)**\(^2\): it’s not the drug that causes addiction, it’s the environment
- **Marc Lewis**\(^3\): addiction is a learned habit that can be unlearned; a developmental disorder not a disease
- **Gene Heyman**\(^4\): most people with addiction do NOT progress or die – most stop when they get older and start making better choices


Two Areas of Brain Research that reinforce the idea that volition can be part of a disease process

1. **Epigenetics**
   Environmentally, behaviorally, and socially-caused DNA modifications, reversible but possibly heritable, that do not change DNA sequence but that can affect gene expression which influences "choice"

2. **Psychoneuroimmunology**
   The interaction between the biopsychosocial functioning of the CNS and the immune system creates a pathological neuroinflammation which plays a key role in mental disorders such as depression & addiction
From the “Disease Model” of Addiction ... 
... to a “Public Health/Ecological Model” of Recovery

The Public Health Model of Recovery
- life course
- educational opportunity
- societal context
- disparity
- family
- social support
- occupation
- cultural context
- faith, meaning and purpose
- political context
- social support
- identity
- mental health
- primary care
- medication
- detox & treatment
- housing
- disparity

Less reductive & can account for
Social Determinants of Health
Health Inequities & Health Injustice

all the causal power of the Disease Model is contained within the Public Health Model ... it is not possible to simultaneously make the argument that addiction is not a disease and advocate for a Public Health approach to addiction

A “Disease” of Volition
- Could such a thing exist? (I’m making an ontologic argument that it can)
- What would happen if such a thing existed? (most advocates for addiction being a disease, especially those who run treatment centers, are making a teleologic argument)
- What is the pathophysiologic nature of volition/free will/choice?
- Is there something special (non-material) about “choice?” If so, what is it?
- If not, then how is “choice” realized in the brain, and how is addiction fundamentally different from any other brain disease process?
- It is very hard for Americans (especially) to accept addiction as a disease because we turn "freedom" into a fetish – for instance, we print words like “Liberty” on our money
The Neuroscience of Addiction in 2023

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The Meadows of Wickenburg
Meadows Behavioral Healthcare

www.protectingsobriety.com

Additional References (1):


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